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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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09/945,131

08/31/2001

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06/02/2004

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EXAMINER

GIBBS, TERRA C

ART UNIT

PAPER NUMBER

1635

DATE MAILED: 06/02/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

849

Office Action Summary

Application No.

09/945,131

Applicant(s)

SIROIS ET AL.

Examiner

Terra C. Gibbs

Art Unit

1635

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 11 March 2004.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1 and 3-20 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1 and 3-20 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 11 March 2004 is/are: a) ☐ accepted or b) ☒ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
 - ☐ Certified copies of the priority documents have been received in Application No. _____.
 - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

This Office Action is a response to Applicants Amendment, Remarks, and Declaration under 37 CFR 1.132, filed March 11, 2004.

Claims 1, 6-9, 11, and 16 have been amended.

Claims 1 and 3-20 are pending in the instant application.

The Examiner would like to point out the list of references contained on pages 39-44 of the Specification. If Applicant intends for the Examiner to consider these references, they must be included on a PTO-1449 Form. Applicant is reminded to follow the rules of MPEP §609, regarding filing an information disclosure statement.

Response to Amendment

Applicants Declaration under 37 C.F.R. §1.132 is acknowledged and has been considered on the merits.

Applicants Amendment to update the reference to priority in the first line of the Specification is acknowledged.

Applicants Drawings, submitted March 11, 2004 are acknowledged. The drawings are objected to because it appears that the instant application contains two sets of drawings labeled as Figures 1-5. For example, the drawings submitted August 31, 2001 contains Figures 1-15. The drawings submitted March 11, 2004 contains Figures 1-5. Therefore, it appears that two sets of drawings labeled as Figures 1-5 are present in the instant application. A proposed drawing correction or corrected drawings are required in reply to the Office action to avoid abandonment of the application. The objection to the drawings will not be held in abeyance.

Art Unit: 1635

Claim Rejections - 35 USC § 112

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 6, 8, 9, 11, and 16 were rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention, in the previous Office Action filed September 8, 2003. **This rejection is withdrawn** in view of Applicants amendments to the claims to correct for insufficient antecedent basis, filed March 11, 2004.

Claims 1 and 3-20 were rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention, in the previous Office Action filed September 8, 2003. **This rejection is maintained** for the reasons of record set forth in the previous Office Action, filed September 8, 2003, and further for the reasons set forth below:

Claims 1 and 5 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The instant claims read on a method for preventing restenosis by improving reendothelialization, vascular endothelial function and by reducing smooth muscle migration and/or proliferation comprising the administration of at least one oligonucleotide complementary

Art Unit: 1635

to a nucleic acid encoding a PDGFR- β subunit, wherein said at least one oligonucleotide further comprises an antisense sequence complementary to the sequence of a gene selected from c-myb, NMMHC, and PCNA.

The claimed invention encompasses nucleic acid compounds encoding all forms of the c-myb, NMMHC, and PCNA genes, which includes sequences from any species, mutated sequences, polymorphic and allelic variants, splice variants, sequences that have an unspecified degree of identity (similarity, homology), and so forth. The specification as filed provides only a description of oligonucleotides complementary to a nucleic acid encoding c-myb, NMMHC, and PCNA (see SEQ ID NOs. 5, 6, and 7, respectively).

The specification as filed provides only a description of oligonucleotides complementary to a nucleic acid encoding c-myb, NMMHC, and PCNA (see SEQ ID NOs. 5, 6, and 7, respectively). However, the specification as filed, does not provide sufficient description that would allow one of skill in the art to use SEQ ID NOs. 5, 6, and 7 to predict the structures of oligonucleotides complementary to a nucleic acid encoding c-myb, NMMHC, and PCNA, respectively, isolated from other sources, including all polymorphic, allelic and splice variants of these mRNA.

The specification fails to describe the complete structure of a representative number of species of the claimed genus. See the Guidelines for Examination of Patent Applications Under the 35 USC 112 ¶ 1, "Written Description" Requirement (Vol. 66, No. 4, pages 1099-1111). These guidelines state that: "To satisfy the written description requirement, a patent specification must describe the claimed invention in sufficient detail that one skilled in the art can reasonably conclude that the inventor had possession of the claimed invention. An applicant shows

possession of the claimed invention by describing the claimed invention with all of its limitations using such descriptive means as words, structures, figures, diagrams, and formulas that fully set forth the claimed invention. Possession may be shown in a variety of ways including description of an actual reduction to practice, or by showing that the invention was “ready for patenting” such as by the disclosure of drawings or structural chemical formulas that show that the invention was complete, or by describing distinguishing identifying characteristics sufficient to show that applicant was in possession of the claimed invention.” In the instant case, the specification does not describe or identify characteristics that can be used to distinguish species of the claimed genus.

Additionally, “[T]he skilled artisan cannot envision the detailed chemical structure of the encompassed polynucleotides and/or proteins, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. The nucleic acid itself is required. See Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993) and Amgen Inc. V. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016. In Fiddes v. Baird, 30 USPQ2d 1481, 1483, claims directed to mammalian FGF's were found unpatentable due to lack of written description for the broad class. The specification provided only the bovine sequence.”

Applicant's specification does not provide a sufficient number of representative species of oligonucleotides complementary to a nucleic acid encoding c-myb, NMMHC, and PCNA, which would allow one of skill in the art to predict the structures of all members of the claimed genus of compounds. One of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus. Therefore, the specification

does not describe the claimed compounds in such full and concise terms so as to indicate that the applicant had possession of these compounds at the time of filing of this application. Applicant is reminded that Vas-Cath makes clear that the written description provision of 35 USC 112 is severable from its enablement provision. (See page 1115.).

Response to Arguments

In response to this rejection, Applicants argue that the present patent specification describes the claimed invention in sufficient details that one of skill in the art can predict the structures of other oligonucleotides. Applicants refer the Examiner to pages to pages 56 and 57 of the Synopsis of Application of Written Description Guidelines published by the USPTO ["Guidelines"] which presents an example of the support required for a claim drawn to an antisense. In that example, the specification did not disclose any antisense sequence. It only disclosed the sequence of the mRNA sequence to which antisense oligonucleotide claimed was complementary. The Guidelines conclude that there is sufficient support for this claim. Applicants argue that the present specification discloses two antisense sequences complementary to a PDGFR- β mRNA. The analysis on which is based this conclusion is as follows. "The procedures for making oligonucleotide fragments of a (sequence) complement are conventional, e.g. any specified fragment can be obtained from a commercial synthesizing service. The procedures for screening for antisense activity are also conventional. The experience accumulated in the art with gene walking is that numerous regions of a target are accessible, that these regions are identified routinely, and that antisense oligonucleotides are complementary to these accessible regions." Applicants argue that sequence of other PDGFR- β species are well

Art Unit: 1635

known in the art and furthermore, this gene is relatively conserved amongst species. Applicants refer the Examiner to the Declaration under 37 CFR §1.132 which presents the alignments between human, mouse, and pig PDGFR- β . Applicants argue that oligonucleotides according to the instant invention from species other than those disclosed in the specification were identified through routine experimentation and effectively used in the methods described in the instant invention.

Applicants argument and Declaration under 37 CFR §1.132 have been considered, but are not found persuasive because while the sequences of several PDGFR- β genes from different species might be well-known and conserved in the art, the claims are broadly drawn to other sequences, including mutated sequences, polymorphic and allelic variants, splice variants, and sequences that have an unspecified degree of identity (similarity, homology) to the PDGFR- β gene. The specification as filed provides only a description of two oligonucleotides complementary to a nucleic acid encoding a PDGFR- β subunit (see SEQ ID NOs. 1 and 2). As argued in the previous Office Action, filed September 8, 2003, the specification as filed, does not provide sufficient description that would allow one of skill in the art to use SEQ ID NOs. 1 and 2 to predict the structures of oligonucleotides complementary to a nucleic acid encoding a PDGFR- β subunit isolated from other sources, including all polymorphic, allelic and splice variants of this mRNA.

The Examiner would like to refer Applicant to the Guidelines for Examination of Patent Applications Under the 35 USC 112 ¶ 1, "Written Description" Requirement (Vol. 66, No. 4, pages 1099-1111). These guidelines state that: "To satisfy the written description requirement, a patent specification must describe the claimed invention in sufficient detail that one skilled in the

Art Unit: 1635

art can reasonably conclude that the inventor had possession of the claimed invention. An applicant shows possession of the claimed invention by describing the claimed invention with all of its limitations using such descriptive means as words, structures, figures, diagrams, and formulas that fully set forth the claimed invention. Possession may be shown in a variety of ways including description of an actual reduction to practice, or by showing that the invention was "ready for patenting" such as by the disclosure of drawings or structural chemical formulas that show that the invention was complete, or by describing distinguishing identifying characteristics sufficient to show that applicant was in possession of the claimed invention." In the instant case, the specification does not describe or identify characteristics that can be used to distinguish species of the claimed genus.

In view of the above, one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus. Therefore, the specification does not describe the claimed compounds in such full and concise terms so as to indicate that the applicant had possession of these compounds at the time of filing of this application.

Claims 1 and 3-20 were rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for inhibiting restenosis by improving reendothelialization, vascular endothelial function, and reducing smooth muscle migration and/or proliferation via the direct delivery of SEQ ID NOs. 1 and 2 to injured carotid arteries, does not reasonably provide enablement for a method for preventing restenosis by improving reendothelialization, vascular endothelial function, and by reducing smooth muscle migration

Art Unit: 1635

and/or proliferation within a blood vessel of a mammal suffering a vascular injury, comprising directly depositing onto a surface or within the blood vessel, at least one oligonucleotide complementary to a nucleic acid encoding a PDGFR- β subunit to injured carotid arteries, wherein at least one oligonucleotide further comprises an antisense sequence complementary to the sequence of a gene selected from the group consisting of c-myb, NMMHC, and PCNA. **This rejection is maintained** for the reasons of record set forth in the previous Office Action, filed September 8, 2003.

Response to Arguments

In response to this rejection, Applicant argue that it is not clear to the Applicant how the Examiner distinguishes “inhibition” and “prevention” in the context of the results presented in the specification. Applicants contend that the model used, namely the rat carotid injury, demonstrated that the used oligonucleotides have diminished the generation of intimal hyperplasia, the best known model for restenosis. In the rat carotid injury model, the oligonucleotides are applied immediately after injury is produced and therefore before intimal hyperplasia has had time to occur. The model is then used to compare the level of intimal hyperplasia produced when oligonucleotides according to the present invention are applied with that produced in a control rat carotid wherein no oligonucleotides were applied. Applicants contend that in order to accelerate prosecution of the present application, claims were amended to use the term “inhibiting” in claim 1 instead of the term “preventing”.

Applicants arguments are moot in view of the amendment to the claims to use the term "inhibiting" in claim 1 instead of the term "preventing". However, this amendment has not overcome the instant rejection.

The instant invention specification provides methodologies for inhibiting restenosis by suppressing intimal thickening and hyperplasia in a rat carotid injury model by restoring endothelium-dependent relaxant function, and reducing smooth muscle migration and/or proliferation via the local endovascular delivery of SEQ ID NOs. 1 and 2 to injured carotid arteries (see Example 2).

The instant specification contemplates the prophylactic use of any oligonucleotide complementary to a nucleic acid encoding a PDGFR- β subunit in restenosis. However, the specification as filed only teaches the inhibition of restenosis by suppressing intimal thickening and hyperplasia in a rat carotid injury model by restoring endothelium-dependent relaxant function, and reducing smooth muscle migration and/or proliferation via the local endovascular delivery of SEQ ID NOs. 1 and 2 to injured carotid arteries. Further, the instant specification contemplates the prophylactic use of any oligonucleotide complementary to a nucleic acid encoding a c-myc, NMMHC, and PCNA in restenosis. However, the specification as filed only teaches the administration of SEQ ID NOs: 5, 6, and 7, corresponding to an antisense oligonucleotides complementary to c-myc, NMMHC, and PCNA, respectively, reduces smooth muscle cell proliferation.

As per the section 112, first paragraph, for lack of written description rejection (see page 3 above), Applicants are not in possession of any oligonucleotide complementary to a nucleic acid encoding a PDGFR- β subunit, other than SEQ ID NOs: 1 and 2. Further, as per the section

Art Unit: 1635

112, first paragraph, for lack of written description rejection above, Applicants are not in possession of any oligonucleotides complementary to a nucleic acid encoding c-myb, NMMHC, or PCNA, other than SEQ ID NOs: 5, 6, and 7, respectively. The specification does not adequately describe the structures and physical properties of those oligonucleotides complementary to a nucleic acid encoding a PDGFR- β subunit, c-myb, NMMHC, and PCNA that can be used to inhibit restenosis, as contemplated in the instant specification. Given its broadest reasonable interpretation, the claims encompass oligonucleotides complementary to a nucleic acid encoding a PDGFR- β subunit c-myb, NMMHC, and PCNA where the specification does not provide sufficient description that would allow one of skill in the art to predict the structures of all nucleic acids that inhibit restenosis, isolated from other sources, including all polymorphic, allelic and splice variants of these mRNA. Thus, it would require undue experimentation to determine what oligonucleotides complementary to a nucleic acid encoding a PDGFR- β subunit, c-myb, NMMHC, and PCNA would act to inhibit restenosis. One of skill in the art would have to engage in undue trial and error experimentation to design oligonucleotides complementary to a nucleic acid encoding a PDGFR- β subunit, c-myb, NMMHC, and PCNA that would inhibit restenosis without the requisite knowledge of primary structures or physical properties. The quantity of experimentation required to practice the invention as claimed would involve the designing of those oligonucleotides encoding a PDGFR- β subunit, c-myb, NMMHC, and PCNA that would inhibit restenosis, by improving reendothelialization, vascular endothelial function, and by reducing smooth muscle migration and/or proliferation, for example. Without specific guidance from the specification, the skilled artisan is left to guess what oligonucleotides possess such activity and to further guess what sequences would elicit an inhibitory response to

Art Unit: 1635

restenosis by reducing smooth muscle migration and/or proliferation, for example. The claims are drawn to a method of inhibiting restenosis by suppressing intimal thickening and hyperplasia in a rat carotid injury model by restoring endothelium-dependent relaxant function, and reducing smooth muscle migration and/or proliferation, where only the local endovascular delivery of SEQ ID NOs. 1 and 2 to injured carotid arteries has been taught to elicit such a response. Further, the claims are so broad to read on a method for inhibiting restenosis by improving vascular endothelial function, where only restoring endothelium-dependent relaxant function is taught (for further explanation, see the 35 U.S.C. 112, second paragraph rejection against claims 1 and 3-20 on page 12 below).

Therefore, in view of the breadth of the claims and the lack of guidance provided by the specification, one of ordinary skill in the art at the time of the invention would have required an undue amount of experimentation to make and use the claimed invention commensurate in scope with these claims.

Claim Rejections - 35 USC § 103

Claims 1 and 3-20 were rejected under 35 U.S.C. 103(a) as being obvious over Rosenberg et al. [U.S. Patent No. 5,593,974] ('974), in view of Rosenberg [WO 93/08845] ('845), as evidenced by Noiseux et al. (Circulation 2000 Vol. 102:1330-1336). **This rejection is withdrawn** in view of Applicants arguments, filed March 11, 2004. Specifically, the Examiner has been persuaded by the arguments that Patent '974 showed that antisense oligonucleotides against c-myc, NMMHC, and PCNA could reduce vascular smooth muscle cells proliferation and intimal thickening, while Application '845 suggested, without experimental data, that

Art Unit: 1635

antisense oligonucleotides could be made against the messengers of PDGFR- β and its vascular receptor to inhibit known activities for this gene. The Examiner has been persuaded further by the arguments that neither Patent '974, nor Application '845 suggest or disclose that PDGFR- β antisense could be used to improve reendothelialization, as these references only described PDGFR- β as a white blood cell recruiter, fibroblast simulator, and smooth muscle cell growth promoter.

It is noted that in response to this rejection, Applicants argued that Noiseux et al. (Circulation 2000 Vol. 102:1330-1336) did not qualify as a prior art reference. The Examiner would like to point out that Noiseux et al. was not being used as a prior art reference, but was instead being used as evidence to support the rejection as being obvious over Rosenberg et al. [U.S. Patent No. 5,593,974] ('974), in view of Rosenberg [WO 93/08845] ('845). At no point in the rejection did the Examiner refer to Noiseux et al. (Circulation 2000 Vol. 102:1330-1336) as a prior art reference.

After reconsideration of the claims, a new ground(s) of rejection is necessitated as presented below:

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Art Unit: 1635

Claims 1 and 3-20 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 is indefinite because it recites the limitation, "a method for inhibiting restenosis by improving reendothelialization, vascular endothelial function, and by reducing smooth muscle migration and/or proliferation". It is unclear how one of ordinary skill in the art can improve vascular endothelial function. The instant specification, at page 34, lines 4 and 5 teach restoring endothelium-dependent relaxant function. However, without a specific definition of "improve vascular endothelial function" one of ordinary skill in the art is not apprised of the metes and bounds of the claim. Claims 3-20 are indefinite for the same reasons due to dependence on claim 1.

Conclusion

Claims 1 and 3-20 are free of the prior art. The closest prior art of record is that of Rosenberg et al. [U.S. Patent No. 5,593,974] and Rosenberg et al. [WO 93/08845] who teach antisense oligonucleotides against c-myc, NMMHC, and PCNA could reduce vascular smooth muscle cells proliferation and intimal thickening, and antisense oligonucleotides could be made against the messengers of PDGFR- β and its vascular receptor to inhibit known activities for this gene, respectively. However, neither reference teaches or suggests that PDGFR- β antisense could be used to improve reendothelialization as instantly claimed.

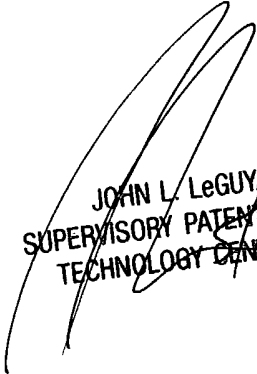
Art Unit: 1635

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Terra C. Gibbs whose telephone number is (571) 272-0758. The examiner can normally be reached on M-F 9:00-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John L. LeGuyader can be reached on (571) 272-0760. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

tcg
May 21, 2004


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